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(21) International Application Number: PCT/US98/01597 (22) International Filing Date: 27 January 1998 (27.01.98) (30) Priority Data: 60/036,542 28 January 1997 (28.01.97) US (71) Applicant: UNITED STATES SURGICAL CORPORATION [US/US]; 150 Glover Avenue, Norwalk, CT 06856 (US). (72) Inventors: ROBY, Mark, S.; 11 Grace Lane, Killingworth, CT 06419 (US). JIANG, Ying; 34 Grandview Terrace, North Haven, CT 06473 (US). (74) Agents: BARRESE, Rocco, S. et al.; Dilworth & Barrese, 333 Earle Ovington Boulevard, Uniondale, NY 11553 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: POLYESTERAMIDES WITH AMINO ACID-DERIVED GROUPS ALTERNATING WITH AL-PHA-HYDROXYACID-DERIVED GROUPS AND SURGICAL ARTICLES MADE THEREFROM (57) Abstract Polyesteramides having amino acid-derived groups alternating with hydroxy acid-derived groups are useful in making shaped articles, particularly, shaped articles suitable for use as surgical devices.		

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POLYESTERAMIDES WITH AMINO ACID-DERIVED GROUPS
ALTERNATING WITH ALPHA-HYDROXYACID-DERIVED GROUPS
AND SURGICAL ARTICLES MADE THEREFROM

5

TECHNICAL FIELD

Polyesteramides with amino acid-derived groups
alternating with alpha-hydroxy-derived groups and methods
for their preparation are described herein. The
polyesteramides are suitable for use in making shaped
articles such as, for example, surgical devices.

15 BACKGROUND

Polyesteramides are polymers containing both ester
linkages and amide linkages. Their significance for
technology of surgical devices stems from the fact that the
susceptibility of their ester linkages to hydrolysis confers
upon them the ability to be eventually absorbed, or resorbed
by a body into which they have been implanted and their
amide linkages confer upon them the desirable mechanical
properties characteristic of polyamides.

Fiber-forming polyesteramides obtained from the
single stage reaction of approximately equimolar amounts of
a monoalkanolamine and a dicarboxylic acid are known from
U.S. Patent No. 2,386,454. Polyesteramides indicated to be
useful for the manufacture of absorbable sutures and other
surgical devices are disclosed in U.S. Patent No. 4,226,243
as obtained from the reaction of a bis-oxyamidodiol (itself
derived from the reaction of diethyl oxalate with a
monoalkanolamine such as ethanolamine) with a dicarboxylic
acid ester. U.S. Patent No 4,343,931 discloses absorbable
surgical devices manufactured from polyesteramides obtained
by reacting a diamine with lactic or glycolic acid to
produce a diamidediol, which is then reacted with a
bischloroformate or a compound selected from the group

consisting of dicarboxylic acids, diacidchlorides and dicarboxylic acid anhydrides.

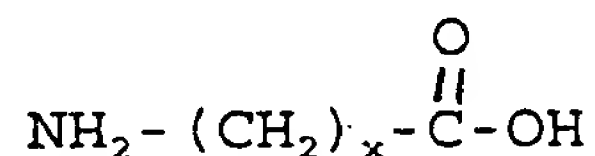
5 Nylon refers to a family of high strength, resilient synthetic materials, the long chain molecules of which contain recurring amide groups. Articles fabricated from nylon have been widely accepted for a variety applications. Certain surgical applications, however, require a surgical device that is bioabsorbable. Nylon is not bioabsorbable and is therefore unacceptable in such
10 circumstances.

It would be desirable to provide a surgical device that has strength and resiliency characteristics similar to those of nylon, but which is bioabsorbable.

15 SUMMARY

It has now been found that polyesteramides having amino acid-derived groups alternating with hydroxy acid-derived groups are useful in making shaped articles, particularly, shaped articles suitable for use as surgical
20 devices.

The polyesteramides are prepared from amino acids of the formula:



25 where x is an integer from 1 to 6; and alpha-hydroxy acids, such as, for example, glycolic acid.

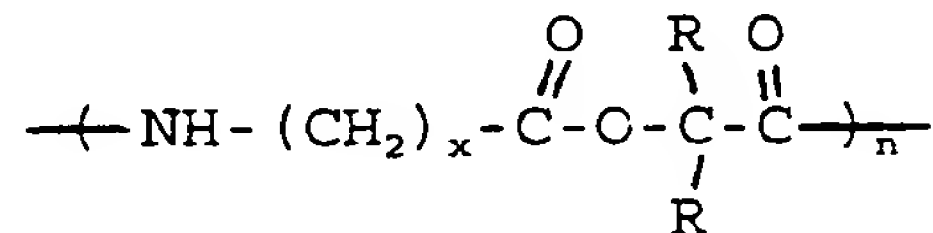
The method of making the present polyesteramides involves blocking the amino group of the amino acid, reacting with an alpha-hydroxy acid, removing the blocking
30 agent and then polymerizing to form the polyesteramide.

The resulting polyesteramide can be bioabsorbable and can be formed into shaped articles, for example by molding or extrusion. Particularly useful shaped articles

include surgical devices such as sutures and other surgical implants.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

5 The polyesteramides described herein are of the
following general formula:



10 wherein x is an integer from 1 to 6 and R can be the same or different at each occurrence and is individually selected from the group consisting of hydrogen and C₁ to C₄ alkyl.

The polyesteramide is prepared from an amino acid of the formula:



where x is an integer from 1 to 6. Preferred amino acids are those wherein x is 1 or wherein x is 5.

The first step in making the polyesteramide is to block the amino group of the amino acid. This will ensure that subsequent chlorination and reaction with the alpha-hydroxy acid occurs only at the acid group of the amino acid. Introduction of a blocking agent onto the amino group can be accomplished using any of the techniques known to those skilled in the art. Suitable blocking agents include benzyl chloroformate. Benzyl chloroformate can be reacted with the amino acid in the presence of a metal oxide (e.g., MgO) in an ice bath of an aqueous ether solution.

The protected amino acid is then converted to an acid halide. This can be achieved, for example, by refluxing the protected amino acid with SOX_2 , wherein X is F, Cl, Br or I in methylene chloride.

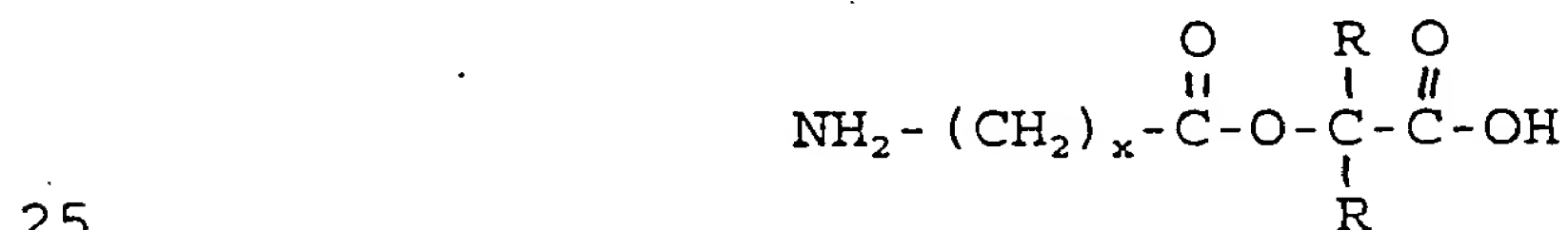
The blocked acid halide is reacted with an alpha-hydroxy acid. Suitable alpha-hydroxy acids include those of the formula:



wherein R can be the same or different at each occurrence and is individually selected from the group consisting of hydrogen and C₁ to C₄ alkyl. Glycolic acid is the preferred alpha-hydroxy acid for making the polyesteramides described herein. The reaction of the acid chloride with the alpha-hydroxy acid can be carried out by refluxing in the presence of an inert diluent such as, for example, DMF and a tertiary amine, such as, for example, triethylamine (TEA).

The blocking agent is then removed from the acid chloride using techniques known to those skilled in the art. For example, if benzyl chloroformate is used as the blocking agent, the blocked acid chloride can be reacted with HBr in acetic acid to remove the blocking agent.

The resulting monomer which is recovered and purified has the general formula:



where x and R are as defined above.

The monomer should be purified, preferably to at least about 98 percent purity. The monomer may be purified using any known technique such as multiple distillations and/or recrystallizations.

The monomer is polymerized by heating to produce a self-condensation reaction. For example, melt polymerization of the monomer prepared from glycine and

glycolic acid can be achieved by heating to around 240 degrees C.

If desired, any portion of the above-described amino acid/ester monomer employed in the polymerization reaction, e.g., from about 1 to about 99 mole percent can be replaced with a like mole percentage of another difunctional, self-condensing comonomer. Such monomers include compounds containing both an acid group and a second active group such as a hydroxy group, an amino group or a second acid group. Thus, by way of example, suitable comonomers include, hydroxycarboxylic acids, diacids and amino acids.

The polyesteramides can be formed into surgical articles using any know technique, such as, for example, extrusion, molding and/or solvent casting. The polyesteramides can be used alone, blended with other absorbable compositions, or in combination with non-absorbable components. A wide variety of surgical articles can be manufactured from the polyesteramides described herein. These include but are not limited to clips and other fasteners, staples, sutures, pins, screws, prosthetic devices, wound dressings, drug delivery devices, anastomosis rings, and other implantable devices. Fibers made from the present polyesteramides can be knitted or woven with other fibers, either absorbable or nonabsorbable to form meshes or fabrics. Compositions including these polyesteramides can also be used as an absorbable coating for surgical devices.

Optional additives which may be present in compositions made from the polyesteramides described herein include plasticizers, release agents and other processing aids. Where the composition is used to make a surgical device, stearic acid or calcium stearate are particularly useful additives due to their biocompatibility.

In another aspect, the compositions containing the polyester amides described herein can be used to make reinforced composites. Thus, for example, the polyesteramide composition can form the matrix of the composite and can be reinforced with bioabsorbable or non-absorbable fibers or particles. Alternatively, a matrix of any bioabsorbable or non-bioabsorbable polymer composition can be reinforced with fibers or particulate material made from compositions containing the polyesteramides described herein.

In an alternative embodiment, the polyesteramides described herein are admixed with a filler. The filler can be in any particulate form, including granulate and staple fibers. While any known filler may be used, hydroxyapatite, tricalcium phosphate, bioglass or other bioceramics are the preferred fillers. Normally, from about 10 grams to about 400 grams of filler are mixed with 100 grams of polymer. The filled, cross-linked polymers are useful, for example, as a molding composition.

It is further contemplated that one or more medico-surgically useful substances can be incorporated into compositions containing the polyesteramides described herein. Examples of such medico-surgically useful substances include, for example, those which accelerate or beneficially modify the healing process when particles are applied to a surgical repair site. So, for example, articles made from compositions containing the present polyesteramides can carry a therapeutic agent which will be deposited at the repair site. The therapeutic agent can be chosen for its antimicrobial properties, capability for promoting repair or reconstruction and/or new tissue growth. Antimicrobial agents such as broad spectrum antibiotic (gentamycin sulfate, erythromycin or derivatized glycopeptides) which are slowly released into the tissue can

be applied in this manner to aid in combating clinical and sub-clinical infections in a tissue repair site. To promote repair and/or tissue growth, one or several growth promoting factors can be introduced into the articles, e.g.,

5 fibroblast growth factor, bone growth factor, epidermal growth factor, platelet derived growth factor, macrophage derived growth factor, alveolar derived growth factor, monocyte derived growth factor, magainin, and so forth. Some therapeutic indications are: glycerol with tissue or

10 kidney plasminogen activator to cause thrombosis, superoxide dimutase to scavenge tissue damaging free radicals, tumor necrosis factor for cancer therapy or colony stimulating factor and interferon, interleukin-2 or other lymphokine to enhance the immune system.

15 It is contemplated that it may be desirable to dye articles made from compositions containing the present polyesteramides in order to increase visibility of the article in the surgical field. Dyes, such as those known to be suitable for incorporation in sutures, can be used. Such

20 dyes include but are not limited to carbon black, bone black, D&C Green No. 6, and D&C Violet No. 2 as described in the handbook of U.S. Colorants for Food, Drugs and Cosmetics by Daniel M. Marrion (1979). Preferably, articles in accordance with this disclosure are dyed by adding up to

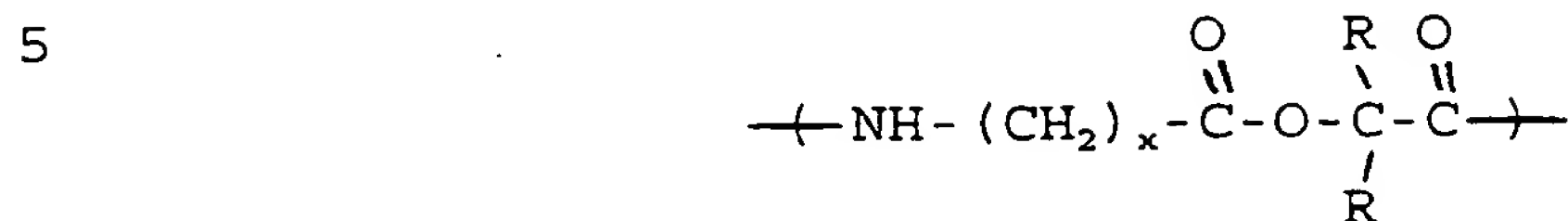
25 about a few percent and preferably about 0.2% dye to the resin composition prior to extrusion.

It will be understood that various modifications may be made to the embodiments disclosed herein. Therefore the above description should not be construed as limiting,

30 but merely as exemplifications of preferred embodiments. Those skilled in the art will envision other modifications within the scope and spirit of the claims appended hereto.

WHAT IS CLAIMED IS:

1. A compound having at least one unit of the general formula:

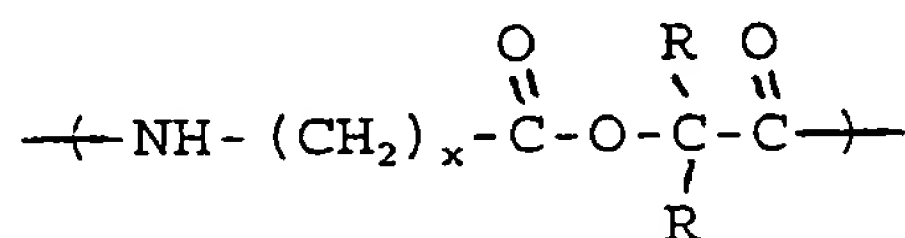


wherein x is an integer from 1 to 6 and R can be the same or different at each occurrence and is individually selected
10 from the group consisting of hydrogen and C₁ to C₄ alkyl.

2. A compound in accordance with claim 1 wherein x is 1 and R at each occurrence is hydrogen.

15 3. A compound in accordance with claim 1 wherein x is 5 and R at each occurrence is hydrogen.

4. A compound in accordance with claim 1 consisting essentially of repeating units of the general
20 formula:



25 wherein x is an integer from 1 to 6 and R can be the same or different at each occurrence and is individually selected from the group consisting of hydrogen and C₁ to C₄ alkyl.

30 5. A compound in accordance with claim 4 wherein x is 1 and R at each occurrence is hydrogen.

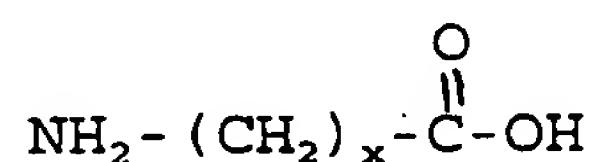
6. A compound in accordance with claim 4 wherein x is 5 and R at each occurrence is hydrogen.

7. A method of making a polyesteramide comprising:

- a) blocking the amino group of an amino acid;
- b) halogenating the blocked amino acid to provide
5 a chlorinated acid;
- c) reacting the halogenated acid with an alpha-hydroxy acid to provide a monomer; and
- d) de-blocking the product of step c);
- e) polymerizing the monomer to produce a
10 polyesteramide.

8. A method in accordance with claim 7 wherein step a) comprises blocking the amino group of an amino acid of the general formula:

15



where x is an integer from 1 to 6.

20 9. A method in accordance with claim 7 wherein step a) comprises reacting an amino acid with benzyl chloroformate.

25 10. A method in accordance with claim 7 wherein step b) comprises reacting the blocked amino acid with a compound of the formula SOX_2 wherein X is selected from the group consisting of F, Cl, Br and I.

30 11. A method in accordance with Claim 7 wherein step b) comprises chlorinating the blocked amino acid.

12. A method in accordance with claim 7 wherein step c) comprises reacting the acid halide with an alpha-hydroxy acid of the general formula:



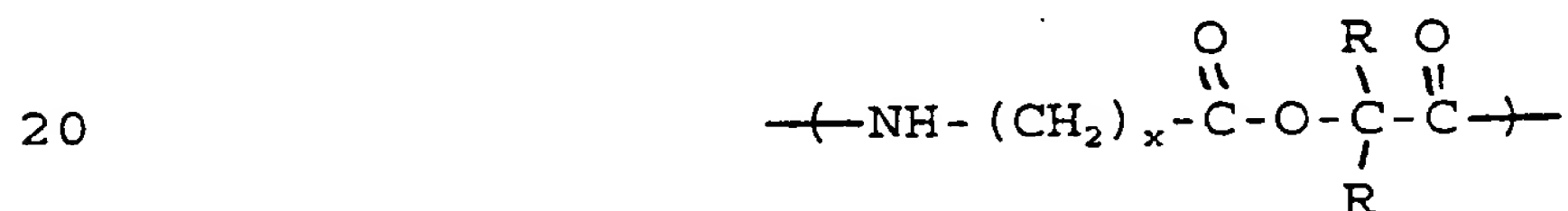
wherein R can be the same or different at each occurrence and is individually selected from the group consisting of hydrogen and C₁ to C₄ alkyl.

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13. A method in accordance with claim 7 wherein step c) comprises reacting the acid halide with glycolic acid.

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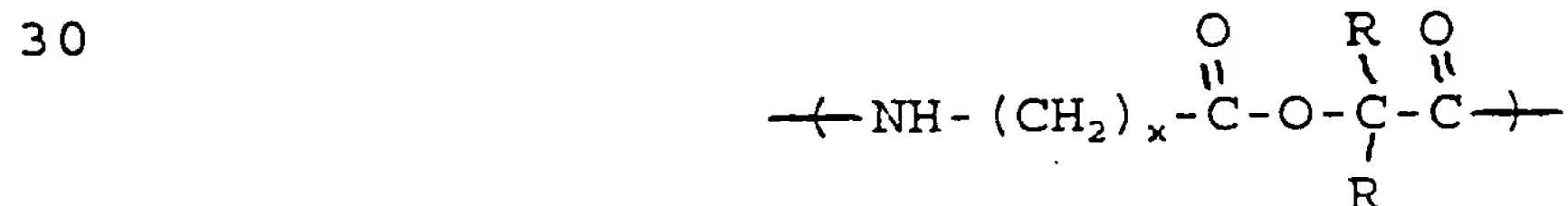
14. A method in accordance with claim 7 wherein the polyesteramide produced in step e) consists essentially of repeating units of the general formula:



wherein x is an integer from 1 to 6 and R can be the same or different at each occurrence and is individually selected from the group consisting of hydrogen and C₁ to C₄ alkyl.

25

15. A composition comprising:
an esteramide compound having at least one unit of the general formula:



wherein x is an integer from 1 to 6 and R can be the same or different at each occurrence and is individually selected from the group consisting of hydrogen and C₁ to C₄ alkyl.

5 16. A composition in accordance with claim 15 further comprising at least one medico-surgically useful compound.

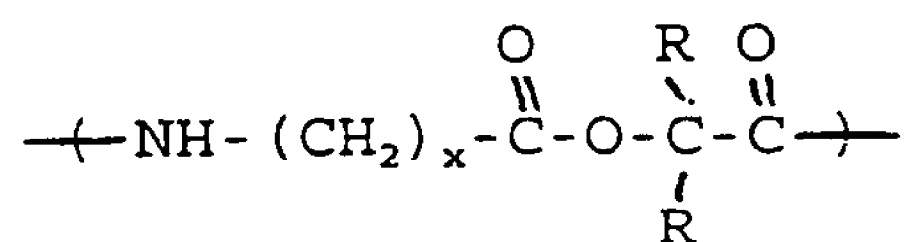
10 17. A composition in accordance with claim 15 further comprising a plasticizer.

18. A composition in accordance with claim 15 further comprising a filler.

15 19. A composition in accordance with claim 15 further comprising one or more bioabsorbable polymer selected from the group consisting of homopolymers and copolymers of glycolide, lactide, trimethylene carbonate, dioxanone and caprolactone blended with the esteramide
20 compound.

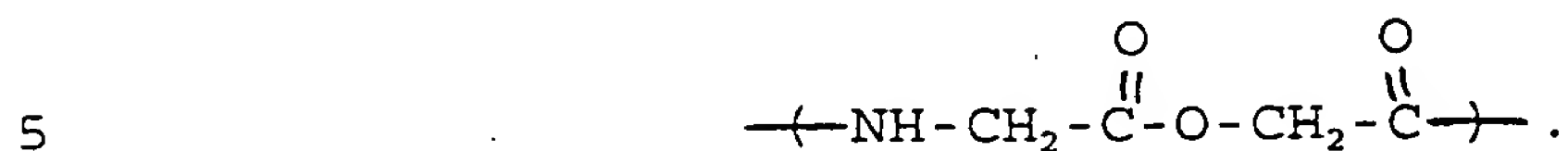
20. A composition in accordance with claim 15 wherein the esteramide compound consists essentially of repeating units of the general formula:

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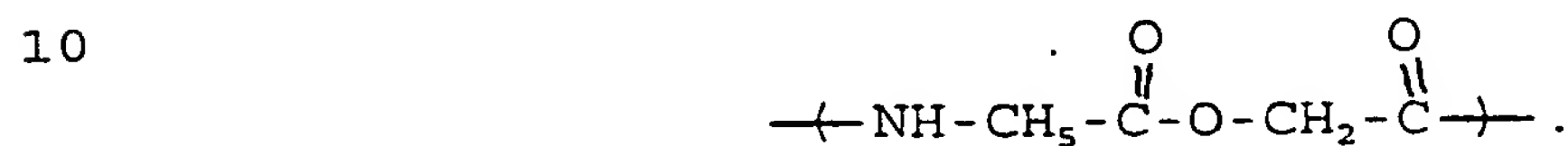


30 wherein x is an integer from 1 to 6 and R can be the same or different at each occurrence and is individually selected from the group consisting of hydrogen and C₁ to C₄ alkyl.

21. A composition in accordance with claim 15 wherein the esteramide compound consists essentially of repeating units of the general formula:



22. A composition in accordance with claim 15 wherein the esteramide compound consists essentially of repeating units of the general formula:



23. A surgical device comprising a shaped article made from the compound of any of claims 1 to 6.

15

24. A surgical device comprising a shaped article made from the composition of any of claims 15 to 21.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/01597

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C08F 283/00; C08G 63/00, 69/28, 73/10; C08L 77/10; A61B 17/10

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
MAYA; AMIDE MONOMER, POLYESTERAMIDE, ESTERAMIDE; SURGICAL DEVICE, ARTICLE; HYDROXY ACID#

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US Re 30,170 A (GOODMAN et al) 18 December 1979, abstract, cols. 11-12.	1-24
Y	US 4,343,931 A (BARROWS) 10 August 1982, abstract, cols. 1-18.	1-24
Y	US 5,349,045 A (JIANG) 20 September 1994, abstract, cols. 1-8.	1-24
Y	US 5,446,108 A (JIANG) 29 August 1995, abstract, cols. 1-6.	1-24
Y	US 5,483,009 A (JIANG) 09 January 1996, abstract, cols. 1-6.	1-24

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

27 MARCH 1998

Date of mailing of the international search report

17 APR 1998

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/01597

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

525/417, 419;
528/ 271, 291, 310, 321, 323, 332, 354, 361, 367, 370, 377, 403, 422;
606/139, 228, 230

B. FIELDS SEARCHED

Minimum documentation searched

Classification System: U.S.

525/417, 419;
528/ 271, 291, 310, 321, 323, 332, 354, 361, 367, 370, 377, 403, 422;
606/139, 228, 230